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Synthesis of optically active polyheterocycles containing pyrrolidine, imidazole and 1,2,3-triazole[1]

Aneta Wróblewska [a,*], Grzegorz Mlostoń [a], and Heinz Heimgartner [b]

[a] Universtity of Łódź, Department of Organic and Applied Chemistry, Tamka 12, PL-91-403 Łódź, Poland

[b] Department of Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

[*]Corresponding author. Tel.: +48 42 6655041.

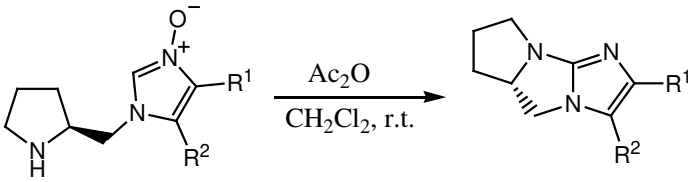
E-mail address: anetka.wroblewska@gmail.com (A. Wróblewska).

Abstract

Optically active polyheterocycles containing pyrrolidine, imidazole and 1,2,3-triazole units were obtained via a multistep synthesis with the [3+2] cycloaddition of Boc-protected (*S*)-(pyrrolidin-2-yl)methyl azide with 2-ethynylimidazoles in the presence of CuI (CuAAC reaction) as the key step. Typical for terminal alkynes, the reactions occurred regioselectively and 1,4-disubstituted 1,2,3-triazoles were formed exclusively. The deprotection of the pyrrolidine N-atom was performed by treatment with TFA under standard conditions.

1. Introduction

Optically active bisheterocycles containing the chiral pyrrolidine skeleton and an imidazole ring can conveniently be prepared from N-protected (*S*)-prolinamine, formaldehyde, and the corresponding α-hydroxyimino ketones.[2] The initially obtained imidazole *N*-oxides of type **1** can by transformed into other imidazole derivatives via deoxygenation, rearrangement, sulfur transfer, and O-alkylation. Recently, the unexpected formation of the polyheterocycles **2** via heterocyclization of bisheterocycles **1**, containing the *N*-deprotected pyrrolidine upon treatment with Ac_2O was reported (Scheme 1).[3]



1 **2**

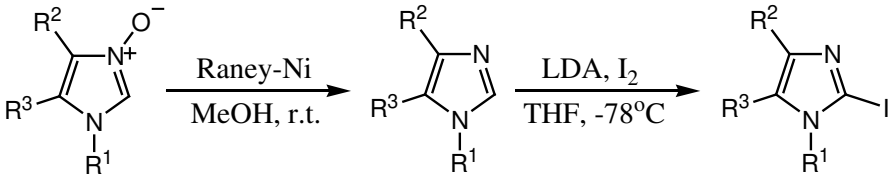
Scheme 1.

On the other hand, the 2-unsubstituted imidazoles are known to undergo ethynylation by treatment of the corresponding 2-iodo derivative with a silylated acetylene in the presence of $Pd(PPh_3)_4$, CuI, and an organic base (Sonogashira-type alkynylation).[4] The obtained 2-ethynylimidazoles were used for the reaction with different azides yielding the 1,2,3-triazole-functionalized imidazoles as biologically active compounds.

In search for optically active polyheterocycles derived from (*S*)-proline, a series of 2-unsubstituted imidazole *N*-oxides of type **1** was used as substrates for the conversion into optically active polyheterocycles containing a 1,2,3-triazole residue along with imidazole and proline units.

2. Results and discussion

The 2-unsubstituted imidazole *N*-oxides **3** were prepared according to the known procedure,[5] and subsequently deoxygenated using Raney-Ni in methanolic solution at room temperature.[6] The imidazoles **4** obtained thereby were treated with LDA in THF at -78 °C and iodinated yielding the desired 2-iodo derivatives **5** (see ref. 4) in good to excellent yields (Scheme 2).

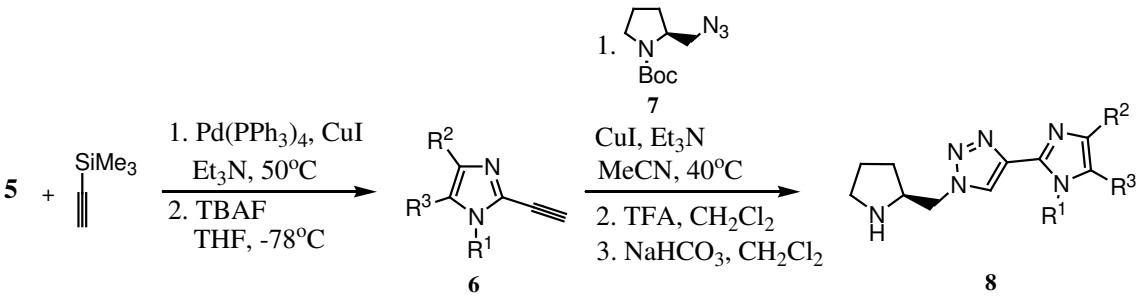


3 **4** **5**

a: R^1=R^2=R^3=Me; **b**: R^1=R^2=Me, R^3=Ph; **c**: R^1=Me, R^2=R^3=Ph; **d**: R^1=Bu, R^2=R^3=Me; **e**: R^1=Bu, R^2=Me, R^3=Ph

Scheme 2.

The next step comprises the reaction of **5** with (trimethylsilyl)acetylene in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI in triethylamine as the solvent at 50 °C. The obtained products were desilylated using tetrabutylammonium fluoride (TBAF). After chromatographic purification, the 2-ethynylimidazoles **6** were isolated and characterized by spectroscopic methods. The most characteristic change in the ^{1}H NMR spectra in comparison with imidazoles **4** was the signal for the acetylenic CH between 3.23 and 3.58 ppm.



a: R^1=R^2=R^3=Me; **b**: R^1=R^2=Me, R^3=Ph; **c**: R^1=Me, R^2=R^3=Ph; **d**: R^1=Bu, R^2=R^3=Me; **e**: R^1=Bu, R^2=Me, R^3=Ph

Scheme 3.

In the final step, the azide **7** derived from the Boc-protected (*S*)-proline was reacted with imidazoles **6** following a 'click' procedure. However, these reactions, performed in acetonitrile solution at 40 °C, required 2 h for complete conversion. The deprotection of the pyrrolidine ring was carried out in a typical manner using TFA in dichloromethane solution. In analogy to Cu(I)-catalyzed cycloadditions of organic azides to non-symmetric acetylenic dipolarophiles, the reactions leading to **8** occurred with complete regioselectivity. Based on the generally known course of these Cu-catalyzed [3+2] cycloadditions with terminal acetylenes,[7] the structure of the sterically less crowded isomers of type **8** was attributed to all products obtained. The regioselectivity of the studied azide-alkyne [3+2]-cycloaddition reactions was unambiguously confirmed by 2D spectroscopic methods. For example, in the case of **8c**, the HMBC spectrum showed the correlation of atoms C(5)*H* of the 1,2,3-triazole ring and *C*H_2 of the N(1)CH_2 bridge. Moreover, correlation of two protons of the N(1)CH_2 group with the C(5) atom of the 1,2,3-triazole unit was also found.

The optically active azide **7** is an attractive building block for the synthesis of optically active 1,2,3-triazoles via the [3+2] cycloaddition with differently substituted acetylenes. Diverse protocols are known for this reaction. Although the classical, non-catalyzed reaction was also reported recently,[8] in general, the cycloaddition was efficiently catalyzed by metal catalysts, such as Cu(I) salts[8a,9,10] and Ru(I) or Ir(I) complexes.[11] Depending on the reaction conditions, the formation of 1,2,3-triazole derivatives occurs with complete regioselectivity or a mixture of the regiosiomers is formed.[8a,11] Typically, bisheterocycles containing a pyrrolidine and a 1,2,3-triazole ring are reported as products obtained with terminal acetylenes. Trisheterocyclic systems were prepared

from **7** and 2-ethynylpyridine[12] and 1-methyl-3-propargylimidazolium chloride,[13], respectively. Using analogous methods, tetra- and pentaheterocyclic compounds with one or two 1,2,3-triazole rings were also synthesized.[12,14]

3. Conclusions

The presented results show that the azide **7** derived from (*S*)-proline can be efficiently used for the preparation of optically active 1,2,3-triazole derivatives of type **8** containing three different *N*-heterocycles. To the best of our knowledge, polyheterocycles of this type are hitherto unknown. They contain three different important heterocyclic units and, therefore, can be considered as attractive model compounds for diverse applications. For example, imidazolyl triazoles were shown to act as inhibitors of biological processes.[4] In addition, they may find applications as proline-derived ligands for asymmetric synthesis and organocatalysts.

4. Experimental

4.1. General

Melting points were determined in a capillary using a Melt-Temp. II apparatus (Aldrich) or STUART SMP30 and are uncorrected. The IR Spectra were recorded on a NEXUS FT-IR spectrophotometer in KBr; absorptions in cm^{-1}. The ^{1}H and $^{13}C\{1H\}$ NMR spectra were measured on a Bruker Avance III instrument (600 and 150 MHz, resp.) using a solvent signal as the reference. The multiplicity of signals in the ^{13}C NMR spectra was established using the HMQC technique. Chemical shifts (δ) are given in ppm and coupling constants J in Hz. Assignments of signals in ^{13}C NMR spectra were made on the basis of HMQC experiments. HR-MS: Bruker maxis spectrometer; ESI-MS: Varian 500. Optical rotations were determined on a PERKIN–ELMER 241 MC polarimeter for λ = 589 nm.

4.2. General procedure for the synthesis of compounds 3

To a solution of imine **1** (0.129 g, 3.0 mmol) in EtOH (4 mL), a solution of an equimolar amount of the corresponding α-hydroxyimino ketone **2** was added and the

reaction mixture was heated at reflux for 3 h. Next, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography or by crystallization.

The synthesis of compounds **3a**[5], **3c**[5], and **3d**[6] was already described in the literature.

4.2.1. 1,4-Dimethyl-5-phenyl-1*H*-imidazole 3-oxide (3b). Yield: 0.374 g (66%). Colorless crystals. Mp. 128–130 °C (Et_2O). IR (KBr): ν 3409br, 3147m, 1636m, 1596m, 1501m, 1443m, 1389m, 1338m, 1164m, 1012m, 857m, 769m, 705m, 645m. ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H, HC(2)); 7.52–7.44 (m, 3H, HC(arom.)); 7.34–7.26 (m, 2H, HC(arom.)); 3.55 (s, 3H, Me); 2.22 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 130.0 (2 CH(arom.)); 129.2 (1 CH(arom.)); 129.0 (2 CH(arom.)); 127.9 (C(5)); 127.3 (C(arom.)); 126.7 (C(4)); 125.9 (C(2)); 33.1 (Me); 7.8 (Me). HR-ESI-MS (MeOH): 189.10224 (calcd 189.10288 for $C_{11}H_{13}N_2O$, $[M+1]^+$).

4.2.2. 1-Butyl-4-methyl-5-phenyl-1*H*-imidazole 3-oxide (3e). Yield: 0.247 g (71%). Colorless crystals. Mp. 82–84 °C (Et_2O). IR (KBr): ν 3385br, 3079m, 2963m, 1630m, 1595m, 1464m, 1383m, 1339m, 1165m, 1014m, 768m, 706m, 641m. ^{1}H NMR ($CDCl_3$): δ 7.97 (s, 1H, HC(2)); 7.52–7.45 (m, 3H, HC(arom.); 7.31–7.26 (m, 2H, HC(arom.); 3.83–3.77 (m, 2H, H_2C); 2.20 (s, 3H, Me); 1.60–1.52 (m, 2H, H_2C); 1.25–1.16 (m, 2H, H_2C); 0.83–0.77 (m, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 130.1 (2 CH(arom.)); 129.3 (1 CH(arom.)); 129.0 (2 CH(arom.)); 127.9 (C(5)); 127.6 (C(arom.)); 126.4 (C(4)); 124.8 (C(2)); 45.8 (CH_2); 32.5 (CH_2); 19.3 (CH_2); 13.2 (Me); 7.7 (Me). HR-ESI-MS (MeOH): 231.14919 (calcd 231.14984 for $C_{14}H_{19}N_2O$, $[M+1]^+$).

4.3. General procedure for the synthesis of compounds 4

To a solution of the corresponding imidazole *N*-oxide **3** (1 mmol) in MeOH (3 mL), a suspension of freshly prepared Raney nickel in MeOH was added. After all of the substrate was consumed (monitored by TLC), the reaction mixture was filtered via celite and the solvent of the filtrate was evaporated. The obtained imidazoles **4** were purified by column chromatography.

The synthesis of compound **4d**[6] was already described in the literature.

4.3.1. 1,4,5-Trimethyl-1*H*-imidazole (4a).[15] Yield: 0.075 g (68%). Colorless oil (SiO_2, AcOEt/MeOH, 8:2). IR (film): ν 3393br, 2921m, 1648m, 1597m, 1509m, 1450m, 1423m, 1390m, 1297m, 1233m, 1185m, 1086m, 970m, 752m. ^{1}H NMR ($CDCl_3$): δ 7.01 (s, 1H, HC(2)); 3.23 (s, 3H, MeN); 1.91 (s, 3H, Me); 1.86 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 135.0 (C(2)); 133.2 (C(5)); 122.4 (C(4)); 31.1 (MeN); 12.5 (Me); 7.9 (Me). HR-ESI-MS (MeOH): 111.09167 (calcd 111.09361 for $C_6H_{11}N_2$, $[M+1]^+$).

4.3.2. 1,4-Dimethyl-5-phenyl-1*H*-imidazole (4b).[16] Yield: 0.107 g (62%). Colorless oil (SiO_2, AcOEt/MeOH, 8:2). IR (film): ν 3382br, 2951m, 1605m, 1579m, 1500m, 1441m, 1302m, 1260m, 1208m, 1080m, 1015m, 968m, 785m. ^{1}H NMR ($CDCl_3$): δ 7.46–7.40 (m, 2H, HC(arom.)); 7.45 (s, 1H, HC(2)); 7.38–7.34 (m, 1H, HC(arom.)); 7.31–7.27 (m, 2H, HC(arom.)); 3.51 (s, 3H, Me); 2.22 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 136.8 (C(2)); 135.7 (C(arom.)); 130.3 (C(5)); 129.8 (2 CH(arom.)); 128.7 (C(4)); 128.6 (2 CH(arom.)); 127.7 (1 CH(arom.)); 32.4 (Me); 13.4 (Me). HR-ESI-MS (MeOH): 173.10732 (calcd 173.10935 for $C_{11}H_{13}N_2$, $[M+1]^+$).

4.3.3. 1-Methyl-4,5-diphenyl-1*H*-imidazole (4c).[15,17] Yield: 0.193 g (82%). Colorless crystals. Mp. 158–160 °C (CH_2Cl_2/hexane). IR (KBr): ν 3432br, 3042m, 1638m, 1601m, 1507m, 1484m, 1444m, 1423m, 1367m, 1316m, 1250m, 1195m, 1068m, 1021m, 953m, 917m, 772m. ^{1}H NMR ($CDCl_3$): δ 7.55 (s, 1H, HC(2)); 7.51–7.47 (m, 2H, HC(arom.)); 7.45–7.40 (m, 3H, HC(arom.)); 7.34–7.31 (m, 2H, HC(arom.)); 7.21–7.17 (m, 2H, HC(arom.)); 7.14–7.10 (m, 1H, HC(arom.)); 3.45 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 138.3 (C(arom.)); 137.5 (C(2)); 134.7 (C(arom.)); 130.7 (2 CH(arom.)); 130.7 (C(5)); 129.0 (2 CH(arom.)); 128.9 (C(4)); 128.6, 128.1, 126.6, 126.3 (6 CH(arom.)); 32.5 (Me). HR-ESI-MS (MeOH): 235.12297 (calcd 235.12457 for $C_{16}H_{15}N_2$, $[M+1]^+$).

4.3.4. 1-Butyl-4-methyl-5-phenyl-1*H*-imidazole (4e). Yield: 0.177 g (83%). Colorless oil (SiO_2, AcOEt/MeOH, 8:2). IR (film): ν 3381br, 2958m, 1606m, 1493m, 1442m, 1380m, 1262m, 1205m, 1114m, 1015m, 968m, 918m, 702m. ^{1}H NMR ($CDCl_3$): δ 7.36 (s, 1H, HC(2)); 7.34–7.29 (m, 2H, HC(arom.)); 7.26–7.22 (m, 1H, HC(arom.)); 7.19–7.15 (m, 2H, HC(arom.)); 3.74–3.69 (m, 2H, H_2C); 2.09 (s, 3H, Me); 1.44–1.37

(m, 2H, H_2C); 1.10–1.04 (m, 2H, H_2C); 0.71–0.66 (m, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 135.9 (C(2)); 135.3 (C(arom.)); 130.5 (C(5)); 129.9, 128.5 (4 CH(arom.)); 128.1 (C(4)); 127.7 (CH(arom.)); 45.0 (CH_2); 32.7 (CH_2); 19.5 (CH_2); 13.3 (Me); 13.1 (Me). HR-ESI-MS (MeOH): 215.15427 (calcd 215.15679 for $C_{14}H_{19}N_2$, $[M+1]^+$).

4.4. General procedure for the synthesis of compounds 5

To a solution of the corresponding imidazole **4** (1 mmol) in dry THF (4 mL), a solution of 1.5 equiv. of LDA in THF was added at –78 ºC. After 1 h, a solution of I_2 in dry THF was added dropwise and the mixture was stirred over night at room temperature. Next, $NH_4Cl_{(aq)}$ was added and the mixture extracted with AcOEt. The organic layers were combined and dried over Na_2SO_4. After filtration, the solvent of the filtrate was evaporated under reduced pressure. The crude products were filtered through a short SiO_2 column.

4.4.1. 2-Iodo-1,4,5-trimethyl-1*H*-imidazole (5a). Yield: 0.158 g (67%). Pale yellow crystals. Mp. 180–182 °C (MeOH/hexane). IR (KBr): ν 3432br, 2918m, 1610m, 1458m, 1438m, 1395m, 1384m, 1274m, 1195m, 1116m, 1086m, 975m, 762m, 718m. ^1H NMR ($CDCl_3$): δ 3.46 (s, 3H, Me); 2.19 (s, 3H, Me); 2.15 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 137.1, 127.0 (C(5), C(4)); 87.4 (C–I); 34.2 (Me); 12.8 (Me); 9.7 (Me). HR-ESI-MS (MeOH): 236.98832 (calcd 236.99005 for $C_6H_{10}N_2I$, $[M+1]^+$).

4.4.2. 2-Iodo-1,4-dimethyl-5-phenyl-1*H*-imidazole (5b). Yield: 0.293 g (98%). Pale yellow crystals. Mp. 110–112 °C (MeOH/hexane). IR (KBr): ν 3422br, 2922m, 1636m, 1493m, 1451m, 1386m, 1282m, 1244m, 1095m, 1014m, 920m, 795m, 753m, 700m. ^1H NMR ($CDCl_3$): δ 7.49–7.45 (m, 2H, HC(arom.)); 7.43–7.39 (m, 1H, HC(arom.)); 7.31–7.26 (m, 2H, HC(arom.)); 3.50 (s, 3H, Me); 2.23 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 137.1 (C(arom.)); 133.0 (C(5)); 130.2, 128.8, 128.7 (5 CH(arom.)); 125.6 (C(4)); 92.4 (C–I); 35.7 (Me); 12.8 (Me). HR-ESI-MS (MeOH): 299.00397 (calcd 299.00539 for $C_{11}H_{12}N_2I$, $[M+1]^+$).

4.4.3. 2-Iodo-1-methyl-4,5-diphenyl-1*H*-imidazole (5c). Yield: 0.231 g (64%). Pale yellow crystals. Mp. 160–162 °C (MeOH/hexane). IR (KBr): ν 3433br, 3066m, 1600m,

1504m, 1452m, 1401m, 1360m, 1296m, 1092m, 1071m, 975m, 915m, 770m, 693m, 602m. ^{1}H NMR ($CDCl_3$): δ 7.46–7.40 (m, 5H, HC(arom.)); 7.30–7.27 (m, 2H, HC(arom.)); 7.18–7.14 (m, 2H, HC(arom.)); 7.13–7.09 (m, 1H, HC(arom.)); 3.39 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 141.6, 133.9 (2 C(arom.)); 132.7, 130.8 (C(5), C(4)); 130.8, 129.1, 129.1, 128.1, 126.7, 126.6 (10 CH(arom.)); 91.6 (C–I); 35.2 (Me). HR-ESI-MS (MeOH): 361.01962 (calcd 361.02049 for $C_{16}H_{14}N_2I$, $[M+1]^+$).

4.4.4. 1-Butyl-2-iodo-4,5-dimethyl-1*H*-imidazole (5d). Yield: 0.153 g (55%). Pale yellow crystals. Mp. 38–40 °C (MeOH/hexane). IR (KBr): ν 3373br, 2958m, 1597m, 1467m, 1417m, 1370m, 1308m, 1210m, 1120m, 1010m, 980m, 765m. ^{1}H NMR ($CDCl_3$): δ 3.80–3.76 (m, 2H, H_2C); 2.20 (s, 3H, Me); 2.15 (s, 3H, Me); 1.66–1.59 (m, 2H, H_2C); 1.42–1.34 (m, 2H, H_2C); 0.99–0.95 (m, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 136.9, 126.4 (C(5), C(4)); 87.3 (C–I); 47.4 (CH_2); 32.4 (CH_2); 19.9 (CH_2); 13.7 (Me); 12.7 (Me); 9.5 (Me). HR-ESI-MS (MeOH): 279.03527 (calcd 279.03650 for $C_9H_{16}N_2I$, $[M+1]^+$).

4.4.5. 1-Butyl-2-iodo-4-methyl-5-phenyl-1*H*-imidazole (5e). Yield: 0.333 g (98%). Pale yellow crystals. Mp. 56–58 °C (MeOH/hexane). IR (KBr): ν 3057br, 2958m, 1606m, 1582m, 1493m, 1459m, 1410m, 1274m, 1016m, 911m, 785m, 756m, 701m. ^{1}H NMR ($CDCl_3$): δ 7.50–7.42 (m, 3H, HC(arom.)), 7.32–7.29 (m, 2H, HC(arom.)), 3.79–3.74 (m, 2H, H_2C); 2.19 (s, 3H, H_3C); 2.14 (s, 3H, H_3C); 1.65–1.58 (m, 2H, H_2C); 1.42–1.34 (m, 2H, H_2C); 0.99–0.94 (m, 3H, H_3C). ^{13}C NMR ($CDCl_3$): δ 137.2, 132.8 (C(5), C(4)); 130.3 (2 HC(arom.)); 129.2 (C(arom.)); 129.9, 128.9 (3 HC(arom.)); 90.4 (C–I); 47.8 (CH_2); 32.4 (CH_2); 19.6 (CH_2); 13.4 (Me); 12.6 (Me). HR-ESI-MS (MeOH): 341.05092 (calcd 341.05239 for $C_{14}H_{18}N_2I$, $[M+1]^+$).

4.5. General procedure for the synthesis of compounds 6

To a solution of the corresponding iodoimidazole **5** (1 mmol), $Pd(PPh_3)_4$ (0.2 mmol), and CuI (0.4 mmol) in dry Et_3N (5 mL), trimethylsilylacetylene (1.2 mmol) was added dropwise. The mixture was heated at 50 ºC until the substrate was consumed (ca. 30 min). Next, the precipitate was filtered and washed with Et_2O. The solvent was evaporated and the crude product was purified by column chromatography (Al_2O_3, AcOEt/hexane 1:9). The obtained product was dissolved in dry THF and TBAF (1.5

equiv.) was added to the solution at –78 ºC. After 20 min, H_2O was added to the mixture, which was then extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and dried over Na_2SO_4. After filtration, the solvent was evaporated. The product **6** was purified by column chromatography (AcOEt/hexane 3:7).

4.5.1. 2-Ethynyl-1,4,5-trimethyl-1*H*-imidazole (6a). Yield: 0.069 g (52%). Pale yellow oil (Al_2O_3, AcOEt/hexane 3:7). IR (KBr): ν 3111br, 2984m, 2098m, 1585m, 1466m, 1405m, 1378m, 1162m, 821m, 746m, 729m. ^{1}H NMR ($CDCl_3$): δ 3.48 (s, 3H, Me); 3.23 (s, 1H, HC); 2.07 (s, 3H, Me); 2.05 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 134.5, 128.6, 124.6 (3 C(imid.)); 80.6, 73.9 (C≡C); 31.1 (Me); 12.7 (Me); 8.9 (Me). HR-ESI-MS (MeOH): 135.09162 (calcd 135.09167 for $C_8H_{11}N_2$, $[M+1]^+$).

4.5.2. 2-Ethynyl-1,4-dimethyl-5-phenyl-1*H*-imidazole (6b). Yield: 0.094 g (48%). Pale yellow oil (Al_2O_3, AcOEt/hexane 3:7). IR (film): ν 3230br, 2918m, 2109m, 1566m, 1487m, 1449m, 1390m, 1018m, 762m, 707m, 655m, 635m. ^{1}H NMR ($CDCl_3$): δ 7.48–7.44 (m, 2H, HC(arom.)); 7.41–7.37 (m, 1H, HC(arom.)); 7.31–7.27 (m, 2H, HC(arom.)); 3.58 (s, 3H, Me); 3.36 (s, 1H, HC); 2.20 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 136.2, 130.2, 130.0, 129.8 (C(arom.), 3 C(imid.)); 129.8, 128.7, 128.2 (5 CH(arom.)); 81.3, 73.8 (C≡C); 32.3 (Me); 13.4 (Me). HR-ESI-MS (MeOH): 197.10756 (calcd 197.10732 for $C_{13}H_{13}N_2$, $[M+1]^+$).

4.5.3. 2-Ethynyl-1-methyl-4,5-diphenyl-1*H*-imidazole (6c). Yield: 0.126 g (49%). Pale yellow oil (Al_2O_3, AcOEt/hexane 3:7). IR (KBr): ν 3299br, 2924m, 2853m, 2118m, 1599m, 1504m, 1478m, 1461m, 1447m, 1387m, 1073m, 964m, 778m, 756m, 697m. ^{1}H NMR ($CDCl_3$): δ 7.53–7.47 (m, 5H, HC(arom.)); 7.38–7.34 (m, 2H, HC(arom.)); 7.24–7.16 (m, 3H, HC(arom.)); 3.57 (s, 3H, Me); 3.44 (s, 1H, HC). ^{13}C NMR ($CDCl_3$): δ 138.6, 133.9, 130.8, 130.3, 130.2 (2 C(arom.), 3 C(imid.)); 130.6, 129.1, 128.9, 128.1, 126.9, 126.7 (10 CH(arom.)); 81.8, 73.6 (C≡C); 32.1 (Me). HR-ESI-MS (MeOH): 259.12283 (calcd 259.12298 for $C_{18}H_{15}N_2$, $[M+1]^+$).

4.5.4. 1-Butyl-2-ethynyl-4,5-dimethyl-1*H*-imidazole (6d). Yield: 0.089 g (51%). Pale yellow oil (Al_2O_3, AcOEt/hexane 3:7). IR (film): ν 3428br, 2958m, 2872m, 2112m, 1735m, 1578m, 1467m, 1410m, 1369m, 1214m, 1007m, 830m, 704m. ^{1}H NMR

($CDCl_3$): δ 3.94–3.89 (m, 2H, H_2C); 3.28 (s, H, HC); 2.14 (s, 3H, Me); 2.13 (s, 3H, Me); 1.70–1.64 (m, 2H, H_2C); 1.39–1.32 (m, 2H, H_2C); 0.94 (*t* = 7.2 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 134.7, 128.4, 123.9 (3 C(imid.)); 80.3, 74.2 (C≡C); 44.6 (CH_2); 32.6 (CH_2); 19.8 (CH_2); 13.6 (Me); 12.8 (Me); 8.9 (Me). HR-ESI-MS (MeOH): 177.13848 (calcd 177.13863 for $C_{11}H_{17}N_2$, $[M+1]^+$).

4.5.5. 1-Butyl-2-ethynyl-4-methyl-5-phenyl-1*H*-imidazole (6e). Yield: 0.099 g (42%). Pale yellow oil (Al_2O_3, AcOEt/hexane 3:7). IR (film): ν 3336br, 2959m, 2123m, 1489m, 1460m, 1405m, 1377m, 1315m, 761m, 702m, 610m, 596m, 508m, 454m. ^1H NMR ($CDCl_3$): δ 7.47–7.43 (m, 2H, HC(arom.)); 7.41–7.38 (m, 1H, HC(arom.)); 7.29–7.26 (m, 2H, HC(arom.)); 3.98–3.94 (m, 2H, H_2C); 3.34 (s, 1H, HC); 2.16 (s, 3H, Me); 1.55–1.49 (m, 2H, H_2C); 1.19–1.12 (m, 2H, H_2C); 0.77 (*t* = 7.2 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 136.3, 130.1, 129.7, 129.5 (C(arom.), 3 C(imid.)); 129.9, 128.7, 128.2 (5 HC(arom.)); 80.9, 74.0 (C≡C); 44.9 (CH_2); 32.5 (CH_2); 19.5 (CH_2); 13.4 (Me); 13.2 (Me). HR-ESI-MS (MeOH): 239.15403 (calcd 239.15428 for $C_{16}H_{19}N_2$, $[M+1]^+$).

4.6. General procedure for the synthesis of compounds 8

To a solution of the corresponding acetylene derivative **6** (1 mmol) and CuI (0.2 mmol) in acetonitrile (3 mL) under argon atmosphere, Et_3N (3 mL) was added. After 15 min, to the yellow reaction mixture was added azide **7**[18] (1 mmol) in acetonitrile (2 mL) dropwise and heated at 40 °C for 2 h. Next, H_2O was added and the mixture was extracted with CH_2Cl_2 (3×15 mL). The organic layers were combined and dry with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was diluted in CH_2Cl_2 (3 mL) and trifluoroacetic acid (1.5 equiv.) in CH_2Cl_2 (2 mL) was added. After all of the intermediate was consumed (monitored by TLC), the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (4 mL). Then, $NaHCO_3$ was added and the mixture was magnetically stirred for 5 h. Next, the solid was filtered and the filtrate was concentrated by evaporation in a rotary evaporator. The crude product **8** was purified by column chromatography.

4.6.1. 4-(1,4,5-Trimethyl-1*H*-imidazol-2-yl)-1-[((*S*)-pyrrolidin-2-yl)methyl]-1,2,3-triazole (8a). Yield: 0.119 g (46%). Pale yellow oil (SiO_2, $CHCl_3$/MeOH 9:1). IR (film): ν 3399br, 2903m, 2824m, 1646m, 1582m, 1459m, 1289m, 1213m, 1013m,

856m, 748m, 618m. ^{1}H NMR ($CDCl_3$): δ 8.22 (s, 1H, HC(triaz.)); 4.46–4.40 (m, 1H, HC); 4.34–4.28 (m, 1H, H_2C); 3.95 (s, 3H, Me); 3.69–3.63 (m, 1H, H_2C); 3.04–2.94 (m, 2H, H_2C); 2.21 (s, 3H, Me); 2.21 (s, 3H, Me); 2.01–1.94 (m, 1H, H_2C); 1.85–1.72 (m, 2H, H_2C); 1.57–1.49 (m, 1H, H_2C). ^{13}C NMR ($CDCl_3$): δ 141.2, 136.9, 133.2, 124.5 (3 C(imid.), C(triaz.)); 123.1 (CH(triaz.)); 57.9 (CH); 55.3 (CH_2); 46.4 (CH_2); 32.1 (Me); 29.1 (CH_2); 25.3 (CH_2); 12.6 (Me); 8.8 (Me). HR-ESI-MS (MeOH): 261.18240 (calcd 261.18222 for $C_{13}H_{21}N_6$, $[M+1]^+$). $[\alpha]_D^{25}$ = –26 (c 0.5, CH_2Cl_2).

4.6.2. 4-(1,4-Dimethyl-5-phenyl-1*H*-imidazol-2-yl)-1-[((*S*)-pyrrolidin-2-yl)methyl]-1,2,3-triazole (8b). Yield: 0.197 g (61%). Pale yellow oil (SiO_2, $CHCl_3$/MeOH 9:1). IR (film): ν 3420br, 2925m, 2854m, 2468m, 1683m, 1635m, 1480m, 1312m, 1203m, 1177m, 1131m, 1048m, 1017m, 833m, 801m, 721m, 703m. ^{1}H NMR ($CDCl_3$): δ 8.53 (s, 1H, HC(triaz.)); 7.37–7.30 (m, 3H, HC(arom.)); 7.16–7.13 (m, 2H, HC(arom.)); 4.71–4.58 (m, 2H, H_2C); 4.01–3.94 (m, 1H, HC); 3.52 (s, 3H, Me); 3.32–3.25 (m, 1H, H_2C); 3.16–3.09 (m, 1H, H_2C); 2.16 (s, 3H, Me); 2.16–2.08 (m, 1H, H_2C); 2.06–1.97 (m, 1H, H_2C); 1.94–1.85 (m, 1H, H_2C); 1.79–1.69 (m, 1H, H_2C). ^{13}C NMR ($CDCl_3$): δ 139.8, 138.9, 134.9, 130.6, 130.1, 129.5, 128.8, 128.1 (C(arom.), 3 C(imid.), C(triaz.), 5 CH(arom.)); 123.2 (CH(triaz.)); 59.9 (CH); 52.9 (CH_2); 45.6 (CH_2); 32.9 (Me); 28.7 (CH_2); 24.1 (CH_2); 12.8 (Me). HR-ESI-MS (MeOH): 323.19803 (calcd 323.19787 for $C_{18}H_{23}N_6$, $[M+1]^+$). $[\alpha]_D^{25}$ = –19 (c 0.625, CH_2Cl_2).

4.6.3. 4-(1-Methyl-4,5-diphenyl-1*H*-imidazol-2-yl)-1-[((*S*)-pyrrolidin-2-yl)methyl]-1,2,3-triazole (8c). Yield: 0.276 g (65%). Pale yellow crystals. Mp. 52–54 °C (MeOH/hexane). IR (film): ν 3424br, 2954m, 2854m, 2202m, 2173m, 1683m, 1602m, 1503m, 1443m, 1400m, 1202m, 1133m, 1055m, 722m, 696m, 640m. ^{1}H NMR ($CDCl_3$): δ 8.45 (s, 1H, HC(triaz.)); 7.44–7.39 (m, 5H, HC(arom.)); 7.34–7.30 (m, 2H, HC(arom.)); 7.20–7.16 (m, 2H, HC(arom.)); 7.15–7.11 (m, 1H, HC(arom.)); 4.60–4.54 (m, 2H, H_2C); 3.83–3.77 (m, 1H, HC); 3.77 (s, 3H, Me); 3.14–3.08 (m, 1H, H_2C); 3.05–2.99 (m, 1H, H_2C); 2.04–1.96 (m, 1H, H_2C); 1.91–1.84 (m, 1H, H_2C); 1.80–1.71 (m, 1H, H_2C); 1.68–1.60 (m, 1H, H_2C). ^{13}C NMR ($CDCl_3$): δ 140.2, 138.9, 137.9 (3 C(imid.)); 134.4, 130.9, 130.8, 130.3, 129.0, 128.7, 128.2, 127.2, 126.7 (2 C(arom.), C(triaz.), 10 CH(arom.)); 124.3 (CH(triaz.)); 58.7 (CH); 53.5 (CH_2); 46.1 (CH_2); 33.1 (Me); 28.9 (CH_2); 24.7 (CH_2). HR-ESI-MS (MeOH): 385.21378 (calcd 385.21352 for $C_{23}H_{25}N_6$, $[M+1]^+$). $[\alpha]_D^{25}$ = –29 (c 0.5, CH_2Cl_2).

4.6.4. 4-(1-Butyl-4,5-dimethyl-1*H*-imidazol-2-yl)-1-[((*S*)-pyrrolidin-2-yl)methyl]-1,2,3-triazole (8d). Yield: 0.117 g (39%). Pale yellow oil (SiO_2, $CHCl_3$/MeOH 9:1). IR (film): ν 3400br, 2968m, 2854m, 1625m, 1562m, 1477m, 1399m, 1286m, 1050m, 812m, 733m, 599m. ^{1}H NMR ($CDCl_3$): δ 8.32 (s, 1H, HC(triaz.)); 4.66–4.57 (m, 1H, H_2C); 4.54–4.46 (m, 1H, H_2C); 4.11–3.99 (m, 2H, H_2C); 3.91–3.82 (m, 1H, HC); 3.45–3.36 (m, 1H, H_2C); 3.23–3.12 (m, 1H, H_2C); 3.19–3.00 (m, 1H, H_2C); 2.12 (s, 3H, Me); 2.09 (s, 3H, Me); 2.06–1.98 (m, 1H, H_2C); 1.96–1.88 (m, 1H, H_2C); 1.85–1.77 (m, 1H, H_2C); 1.69–1.60 (m, 1H, H_2C); 1.57–1.37 (m, 3H, H_2C); 0.85 (*t* = 7.2 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 139.7, 136.4, 132.9, 124.0 (3 C(imid.), C(triaz.)); 122.9 (CH(triaz.)); 59.1 (CH); 54.4 (CH_2); 53.3 (CH_2); 45.7 (CH_2); 44.6 (CH_2); 32.6 (CH_2); 28.9 (CH_2); 24.4 (CH_2); 13.6 (Me); 12.2 (Me); 8.7 (Me). HR-ESI-MS (MeOH): 303.22922 (calcd 303.22917 for $C_{16}H_{27}N_6$, $[M+1]^+$). $[\alpha]_D^{25}$ = –32 (c 0.5, CH_2Cl_2).

4.6.5. 4-(1-Butyl-4-methyl-5-phenyl-1*H*-imidazol-2-yl)-1-[((*S*)-pyrrolidin-2-yl)methyl]-1,2,3-triazole (8e). Yield: 0.174 g (48%). Pale yellow oil (SiO_2, $CHCl_3$/MeOH 9:1). IR (film): ν 3398br, 2953m, 2862m, 1614m, 1538m, 1443m, 1402m, 1279m, 1039m, 829m, 730m, 608m. ^{1}H NMR ($CDCl_3$): δ 8.21 (s, 1H, HC(triaz.)); 7.42–7.37 (m, 2H, HC(arom.)); 7.35–7.31 (m, 1H, HC(arom.)); 7.28–7.25 (m, 2H, HC(arom.)); 4.40–4.22 (m, 4H, H_2C); 3.67–3.56 (m, 1H, HC); 2.96–2.84 (m, 2H, H_2C); 2.12 (s, 3H, Me); 1.93–1.86 (m, 1H, H_2C); 1.77–1.66 (m, 2H, H_2C); 1.48–1.40 (m, 3H, H_2C); 1.09–1.01 (m, 2H, H_2C); 0.63 (*t* = 7.2 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 140.9, 135.3, 130.7, 130.1, 125.9 (3 C(imid.), C(arom.), C(triaz.)); 130.4 (2 HC(arom.)); 128.6, 127.9 (3 HC(arom.)); 123.6 (CH(triaz.)); 61.8 (CH); 55.3 (CH_2); 46.5 (CH_2); 44.9 (CH_2); 32.9 (CH_2); 29.2 (CH_2); 25.4 (CH_2); 19.3 (CH_2); 13.4 (Me); 13.1 (Me). HR-ESI-MS (MeOH): 365.24494 (calcd 365.24482 for $C_{21}H_{29}N_6$, $[M+1]^+$). $[\alpha]_D^{25}$ = –16 (c 0.625, CH_2Cl_2).

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